



Regulation of Human Tissue for Transplantation

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Historically the Food and Drug Administration has not regulated human tissues for transplantation, but with the pervasive scourge of AIDS and widespread public concern about preventing its transmission, pressure has mounted on the government to introduce more specific regulatory controls over the tissue industry. This paper will document the development since 1990 of the movement to achieve such controls, by examining Congressional legislation, FDA activity, testimony of important figures involved in the debate, and industry trends. The discussion will be confined for the most part to human tissue as distinct from blood or organs, upon which exhaustive research would be beyond the scope of this effort.

What changed?

Over the last fifteen years, three important developments in the use of human tissue for transplantation laid the groundwork for what would become the movement for more direct comprehensive governmental regulation in the area. The first was a technological explosion. When technology was less advanced, the only medically viable options for tissue transplantation were recovery of fresh human tissue for immediate use in a patient in need, with little or no processing. In those cases the questions about potential harm from handling, processing, or chemical contamination were few. Advances in chemical technology and cryopreservation, however, permitted groundbreaking treatment of tissues in order to preserve them for longer time periods and thereby introduced new concerns about contamination, deterioration, and efficacy.

The technological advances in turn spawned another explosion - this time a commercial one. As preservation technology spread, so did new storage and transportation techniques. Distribution of tissues, previously handled only locally, soon expanded into nationwide networks of tissue banks capable of storing tissues for long time periods and delivering them in short order. Tissue banking became a popular, lucrative, national proposition.

At the same time tissue banking expanded during the 1980s, no health issue was of more public importance or interest than the spread of HIV/AIDS. The American public came to view the disease as of epidemic proportions, and the rapidity with which government and private institutions sought to educate society about the disease was unprecedented in modern times and continues today.

Together, these three developments created fertile territory for a potential groundswell of public and legislative interest in heightened governmental regulation of the tissue banking industry. By the early 1990s the federal government was indeed enforcing some regulation under the 1976 Medical Device Amendments, but it was non-comprehensive, “pick-and-choose” regulation of only certain types of tissues, namely dura mater (fibrous tissue surrounding the brain and spinal cord), corneal lenticules, and heart valves. And as is the case with most movements for governmental change, the potential forces described above were by themselves insufficient to effect more comprehensive regulation - they needed a catalyst.

Three events catalyzed the momentum for Congressional re-examination of

regulating the human tissue industry. The first was the devastating discovery in 1991 that Mr. William Norwood, an organ and tissue donor who had been fatally shot in a 1985 gas station holdup, was HIV-positive. Fifty-eight individuals received organs and tissues from Mr. Norwood; three patients who received organs from him died from AIDS-related conditions, and three who received tissue grafts tested HIV-positive.¹

The second event was a 1991 FDA Notice of Applicability of a Final Rule (NAFR)² issued to clarify that heart valve allografts were to be considered Class III medical devices for regulatory purposes. In short, the FDA decided to regulate heart valve allografts exactly as it was already regulating replacement heart valves. Such valves (and with the 1991 regulation, allografts as well) were subject to a 1987 FDA rule requiring filing of a premarket approval application (PMA).³ Classification of replacement heart valves is found at 21 C.F.R. §870.3925(a), and the regulation concluded that replacement heart valve allografts “squarely fit within the agency’s classification regulation...”⁴ Further, FDA concluded that any distribution of the allografts was to be under an investigational device exemption (IDE) for significant risk devices.⁵

The third catalyzing event was a Seventh Circuit decision supporting the FDA regulation. In *Alabama Tissue Center v. Sullivan*, 975 F.2d 373 (7th Cir.

¹Tracy Walmer, *Virginia Community Tries to Make Sense of AIDS Donor Mystery*, USA TODAY, May 22, 1991, at 2A.

²56 Fed. Reg. 29,177 (1991).

³52 Fed. Reg. 18,162 (1987).

⁴56 Fed. Reg. 29,177, 29,178 (1991).

⁵*Id.*

1992), six tissue banks asked the court to overturn the FDA's rule classifying human heart valves as medical devices, but the court dismissed the petition. The tissue banks felt that compulsory filing of IDEs for allograft heart valves which had already been used successfully in thousands of patients over several years was an unreasonable mandate. The court held that since the FDA assumed authority over the valves in a Notice of Applicability of a Final Rule, an interpretative rule and not a regulation, such FDA action was not subject to appellate review.⁶

The Human Tissue Transplantation Act of 1992

This chain of events prompted Congressional action. On June 29, 1992 Senator Paul Simon of Illinois introduced the Human Tissue Transplantation Act of 1992.⁷ The bill failed to pass, but as the first explicit proposal of direct federal regulation of human tissue, its content as well as the testimony of several key figures at a hearing to consider it revealed important arguments that continue to define the debate in this area.

The bill proposed several new means of regulation. It imposed a licensing scheme for tissue banks as well as creation of a National Council on Tissue Transplantation.⁸ The Council was to be a nonprofit entity whose duties included collection, analysis, and dissemination of data concerning human tissue donation and transplants, increasing availability of tissue types in short supply,

⁶Alabama Tissue Center v. Sullivan, 975 F.2d 373, 379 (1992).

⁷S. 2908, 102d Cong., 2d Sess. (1992).

⁸*Id.* § 355.

development of uniform record-keeping methods, and development of voluntary professional standards to assure that donated human tissue would not transmit disease.⁹ The bill also authorized inspections of tissue banks to ensure conformance with licensing requirements¹⁰ and provided that if the Secretary (of Health and Human Services) found the voluntary standards developed by the Council for a particular tissue to be inadequate, then he would be authorized to establish a public standard for the tissue.¹¹ The public standard would include provisions applying to the processing, physical and biological properties, and labeling for each tissue type.¹² Finally, enforcement options for various violations included civil penalties ranging from \$10,000 to \$50,000 per violation, license suspension, and seizure of human tissue violative of the standard.¹³

Following introduction of the bill in the Senate, a hearing was held on September 29, 1992 before the Senate Labor and Human Resources Committee. In his opening statement at that hearing, Committee Chairman and Senate Bill 2908 sponsor Senator Simon noted the absence of any national tissue standards or tissue bank oversight, and dismissed the June 1991 FDA action as “regulatory overkill.”¹⁴ Next the Senator mentioned the three general principles he had in mind in drafting the legislation:

First, both the tissue bank community and the federal government have the responsibility to the public to assure the safety of human tissue. Second, human tissue should not be regulated as if it is an artificial product designed by

⁹*Id.*

¹⁰*Id.* § 357.

¹¹*Id.* § 358.

¹²*Id.*

¹³*Id.* § 359.

¹⁴*Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Comm. on Human Resources*, 102d Cong., 2d Sess. 1 (1992) (statement of Sen. Paul Simon).

human beings. And third, the regulation of human tissue should be by a single regulatory mechanism developed either through statute or by an agreement among the FDA and the transplantation community.¹⁵

FDA Deputy Commissioner for Policy Michael R. Taylor then testified to the FDA's position on Senate Bill 2908 and on generally what should be addressed in devising a tissue regulation scheme. While ultimately concluding that Senate Bill 2908 was not comprehensive enough to win the FDA's full support, Mr. Taylor nevertheless praised Congressional interest and effort in the area of human tissue regulation and made some important statements regarding FDA's position on the issue.

First, he mentioned the recommendation of a 1991 Public Health Service (PHS) task force (organized after the Norwood incident, see *supra* p. 2) that the FDA establish at least a mandatory floor of requiring registration of tissue banks, setting donor screening criteria, and establishing record-keeping measures to track tissues.¹⁶ Mr. Taylor said that the FDA found the safety-related measures recommended by PHS to be "an appropriate part of any new Federal regulatory scheme for tissues," but hedged, adding that any regulatory floor must be considered "in the context of the broader set of safety, effectiveness, and resource issues..."¹⁷

Second, Mr. Taylor touched on the history of FDA regulation in the

¹⁵ *Id.*

¹⁶ *Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Comm. on Human Resources*, 102d Cong., 2d Sess. 4 (1992) (statement of Michael R. Taylor, FDA Deputy Commissioner for Policy).

¹⁷ *Id.*

area, specifically referring to heart valve allografts, and described the costs and benefits of FDA regulatory controls in general. He noted in particular the difficult and disruptive effect that imposition of FDA regulation has had on products with well-established therapeutic roles. The benefits of standardization and medical safety notwithstanding, he argued, any efficiency calculus must take into account the twin goals of safety and continued access to critical life saving tissue. He also noted the special difficulty of retrospective application of a new federal standard to the numerous already-functioning tissue banks in the United States.¹⁸

In summarizing FDA's position, he outlined three broad questions that continue to define the tissue regulation debate:

First, is there a need for a comprehensive Federal program instead of the case-by-case application of FDA's medical device or biologics authority? If there is a need, should it be addressed under current law or through new legislation tailored to tissues? And finally, what are the appropriate elements for a regulatory scheme for tissues?¹⁹

To the first question Mr. Taylor answered that the public health concern is one possible justification for a more comprehensive federal program, but that the FDA was continuing to examine the "full array" of public health issues before it.²⁰ In essence, then, to this first important question the FDA's answer was only that it had not yet determined whether there was a need for comprehensive federal regulation.

To the second question, he explained that the FDA's position was that it had authority "under the Public Health Service Act and the Food and Drug Act,

¹⁸ *Id.* at 6.

¹⁹ *Id.*

²⁰ *Id.* at 7.

to mount just about any regulatory intervention one might reasonably consider appropriate.” He continued, however, to note the growing suggestion that tissues are sufficiently different from medical devices to warrant specially tailored legislation, and hinted that the FDA was leaning toward this conclusion, assuming it were determined that a need for comprehensive federal regulation existed at all.²¹

To the third and final question of what the FDA deemed would comprise an appropriate regulatory scheme, Mr. Taylor’s answer emphasized that any acceptable scheme would have to be flexible, but that it must address the following at a minimum: safety; standards to assure product quality; administrative treatment of new processes and tissue uses; involvement of private standard setting and oversight bodies; and enforcement. He cited in particular the failure of Senate Bill 2908 to address the third of these concerns, namely the establishment of safety and effectiveness criteria for new medical technologies.²²

Dr. S. Randolph May, National Head of Tissue Services for the American Red Cross, also testified to the Committee. After briefly recounting the horrors of the Norwood tragedy, he emphasized that the voluntary regulation that governed the tissue banking industry, while helping somewhat to provide safe, quality tissue, was in the aftermath of Norwood clearly inadequate. He then made a powerful plea on behalf of the Red Cross for swift and strong Congressional action:

²¹ *Id.*

²² *Id.*

The American Red Cross feels strongly that mandatory, enforceable standards are needed to assure the safety of the people who depend upon transplantable human tissue to sustain or improve the quality of their lives. . . . The American Red Cross urges Congress to establish a public law that requires enforceable regulations with the aim of preventing the transmission of diseases such as AIDS and hepatitis through tissue transplantation.²³

The last major figure to testify was one from within the tissue banking industry itself, Dr. Charles Cuono, President of the American Association of Tissue Banks (AATB). He announced three principles the AATB found fundamental to any regulatory scheme: compulsory registration of all tissue banks, establishment of uniform donor screening criteria, and establishment of a tracking system. He concluded that Senate Bill 2908 failed to adequately address these issues, primarily due to its reliance on the National Council on Tissue Transplantation and voluntary professional standards. Further, he argued that Senate Bill 2908 would only duplicate (at taxpayer expense) the existing voluntary system of the AATB.²⁴

Taken together, Senate Bill 2908 and the testimony of these three critical “players” revealed some noteworthy trends. First, all agreed that the concern of paramount importance was safety. Exactly how to assure it was the problem, but agreement on its primacy as a goal is nonetheless important. Second, all agreed that some uniformity of standards would be desirable - whether it should be achieved via voluntary or compulsory standards was contested -

²³*Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Comm. on Human Resources*, 102d Cong., 2d Sess. 14, 15 (1992) (statement of S. Randolph May, National Head of Tissue Services, American Red Cross).

²⁴*Regulation of Human Tissue Transplantation: Hearing on S. 2908 Before the Senate Comm. on Human Resources*, 102d Cong., 2d Sess. 17 (1992) (statement of Charles B. Cuono, President, American Association of Tissue Banks).

but again, this was only a first step in public discourse. Finally, all agreed that a uniform record-keeping and tracking system should be established. All told, this was a substantial zone of agreement, especially considering Senate Bill 2908 was the first Congressional attempt at direct legislation of the tissue industry. It was perhaps this generally favorable response that prompted Senator Simon and others to try again in 1993.

Round II: The 1993 Hearings

On October 15, 1993, Representative Ron Wyden of Oregon chaired a subcommittee hearing on the regulation of human tissue banks. Around two weeks before the hearing, however, the subcommittee staff prepared an important memorandum for Representative Wyden concerning human tissue regulation. The memorandum was the result of a two-year long investigation commissioned by Representative Wyden to inquire into “the safety and effectiveness of non-organ human tissues which are harvested and processed for transplantation purposes.”²⁵

In conducting their inquiry, the subcommittee staff met with government officials as well as representatives from private companies (both for-profit and non-profit), and visited several tissue processing and storage facilities. Their conclusions were similar to those of the witnesses at the 1992 hearings: first, though the human tissue network seemed relatively disease-free, contaminated tissue remained a threat to public health. This, they concluded, was largely due to poor record-keeping, faulty testing, and inconsistent standards. Second,

²⁵STAFF OF SUBCOMM. ON REGULATION, BUSINESS OPPORTUNITIES AND TECHNOLOGY OF THE HOUSE COMM. ON SMALL BUSINESS, 103D CONG., 1ST SESS., MEMORANDUM ON THE REGULATION OF HUMAN TISSUE FOR TRANSPLANT (1993).

assuring effectiveness of tissue (aside from disease contamination) that might undergo varying chemical and cryogenic preservation techniques was woefully unaddressed, again due to the paucity of widely-accepted industry standards. Third, they noted the acknowledgment of public health agencies, including the FDA, that then-current regulatory methods were “inadequate, outdated, and often in conflict.”²⁶ Finally, they recommended a mandatory program with the following now-familiar elements at a minimum: registration of all tissue banks; uniform tissue banking practices (including testing and processing standards); and tracking methods to trace tissue from donor to recipient.²⁷

At the hearing on October 15, 1993 several of the witnesses from the 1992 hearing were present again. But unlike Senator Simon, Representative Wyden included some powerful rhetoric in his opening statement arguing for the need for regulatory change:

It is time to stop gambling against the odds when health officials fail to test tissue. The transmission of HIV, Hepatitis-C and Creutzfeldt-Jakob disease has dealt a painful blow to the safety reputation of tissue transplants.

It’s unacceptable that the U.S. health system cannot locate infected patients because tissue has not been tracked.

Inadequate donor screening is unfair to patients. . . . Our government has learned tragic safety lessons about the need to stop the spread of infectious disease through preventive measures.²⁸

He then unleashed an assault on the inadequacy of then-current federal policy, attacking regulation of corneas, heart valves and dura mater as an ineffective patchwork resulting in “a regulatory brake on needed research and development

²⁶ *Id.*

²⁷ *Id.*

²⁸ *Regulation of Human Tissue Banks: Hearing Before the Subcomm. on Regulation, Business Opportunities and Technology of the House Comm. on Small Business*, 103d Cong., 1st Sess. (1993) (statement of Rep. Ron Wyden).

in the industry.”²⁹

Testifying on behalf of the FDA this time was Dr. Kathryn Zoon, Director of the FDA Center for Biologics Evaluation and Research (CBER). Her testimony was in many respects similar to that of Mr. Taylor in 1992, but it also revealed some important new FDA input. Areas of similarity included a conviction that infectious disease transmission and effectiveness of preserved donated tissue were of paramount concern, and that establishment of uniform standards would help minimize their associated risks. She also echoed Mr. Taylor’s emphasis on the need for effective enforcement, but unlike him explicitly stated a need to rely less on product specific, case-by-case approvals and more on generally acceptable uniform public standards.³⁰

Dr. Zoon also announced several new issues that the FDA considered critical. First, she urged that any legislation must address resources and funding for a new regulatory effort and argued that user fees should bear the majority of the cost.³¹ Second, more than any witness at previous hearings, she addressed the effects rapid commercialization was having on the industry and on the need to regulate. She argued that tissue banks’ frequent exaggeration of tissue product benefits and failure to provide balanced risk information in promotional mate-

²⁹ *Id.*

³⁰ See *Regulation of Human Tissue Banks: Hearing Before the Subcomm. on Regulation, Business Opportunities and Technology of the House Comm. on Small Business*, 103d Cong., 1st Sess. (1993) (statement of Kathryn Zoon, Director, FDA Center for Biologics Evaluation and Research).

³¹ See *id.*: “The standard setting and other functions of a federal oversight program would provide real value to the tissue banking community in terms of public credibility and a level playing field, and it is fair to ask that community to bear the cost.”

rials necessitated FDA monitoring of not only advertising and promotion, but also of labeling. Third, she emphasized the practical reality of the need to maintain altruistic donation of human tissue. By assuring the safety and reliability of tissue, she argued, federal regulatory oversight would encourage altruism by making people more confident about the usefulness of their donated tissue.³²

Dr. May once again testified on behalf of the Red Cross, reiterating its position strongly favoring the imposition of federal standards and enforcement. He favored a system of mandatory registration and licensing of tissue banks, establishment of tissue-specific donor screening procedures, and development of an effective tracking system.³³

The AATB was once again represented at the hearing, this time by Dr. D. Ted Eastlund. He acknowledged that despite general success of the voluntary standards his organization imposed, federal oversight would provide needed enforcement power and uniformity. The AATB, like the Red Cross and the FDA, supported registration of tissue banks, uniform donor screening and tissue standards, and a nationwide tracking scheme. Unlike the FDA, however, (and not surprisingly) the AATB did not support funding the regulatory program with user fees - Dr. Eastlund warned that tissue banks could not absorb such costs without passing them on to patients in need of the tissues. Finally, the AATB argued for exemption from premarket approval for tissues already in common use, and more specifically for the deletion of human heart valves from

³² See *id.*

³³ See *Regulation of Human Tissue Banks: Hearing Before the Subcomm. on Regulation, Business Opportunities and Technology of the House Comm. on Small Business*, 103d Cong., 1st Sess. (1993) (statement of S. Randolph May, National Head of Tissue Services, American Red Cross).

the Class III medical device classification and their inclusion in the provisions of the new legislation.³⁴

The 1993 hearing was an important follow-up to the groundbreaking 1992 hearing, and the witness testimony from the key agencies revealed both significant consistency of opinion from each agency as well as productive new thoughts and suggestions about how successful legislation might be tailored. Senator Simon and Representative Wyden responded not long thereafter.

The Human Tissue for Transplantation Act of 1993

On November 19, 1993, Senator Simon introduced Senate Bill 1702³⁵ in the Senate. On the same day, Representative Wyden introduced substantially identical legislation in the House, House Bill 3547.³⁶ The bill in both houses was called the “Human Tissue for Transplantation Act of 1993.” Ultimately the bill would pass in neither house, but a survey of its content sheds some light on the historical development of regulation attempts.³⁷

The first important difference between this new proposal and the Human Tissue Transplantation Act of 1992 was that the 1992 legislation proposed to amend the Public Health Service Act, while the 1993 bill proposed to amend the Food, Drug, and Cosmetic Act. This likely indicated a more direct charge to FDA to carry out the regulation than was present in the 1992 bill.

House Bill 3547 differed from the 1992 bill in significant substantive

³⁴See *Regulation of Human Tissue Banks: Hearing Before the Subcomm. on Regulation, Business Opportunities and Technology of the House Comm. on Small Business*, 103d Cong., 1st Sess. (1993) (statement of D. Ted Eastlund, President, American Association of Tissue Banks).

³⁵S. 1702, 103d Cong., 1st Sess. (1993).

³⁶H.R. 3547, 103d Cong., 1st Sess. (1993).

³⁷For simplicity’s sake, citations will be to H.R. 3547 alone, since both it and S. 1702 were substantially identical.

ways as well. It furnished basic definitions, including ones for “tissue,” “banked human tissue,” and “human tissue bank.”³⁸ It created authority for the FDA to require tissue screening, donor testing, and record-keeping and mandated FDA establishment of “good tissue banking practice.”³⁹ New labeling and advertising requirements were authorized, as well as implementation of a tissue bank registration and licensing scheme.

To tap the insight and experience of the private sector, House Bill 3547 directed establishment of a national “Tissue Advisory Committee” whose functions would include advising the Secretary on appropriate standards of quality and handling for various tissue types, reporting on new technological developments in the industry, and assisting in establishing a system of investigating consumer complaints.

As for enforcement, the full range of options available for drugs and devices would be made available for tissues as well, including civil penalties, criminal prosecution and seizures.⁴⁰ Funding of House Bill 3547’s scheme was to be derived from user fees collected from each tissue bank as a condition of its registration.⁴¹ Finally, the bill would have nullified the infamous 1991 NAFR subjecting human heart valve allografts to premarket approval.⁴²

The 1993 legislation was a more sophisticated attempt to produce new federal tissue regulation than its predecessor, and its authors clearly benefited from and incorporated many of the ideas and suggestions advanced at the in-

³⁸H.R. 3547, 103d Cong., 1st Sess. § 3 (1993).

³⁹*Id.* § 4.

⁴⁰*See id.* § 5.

⁴¹*See id.* § 6.

⁴²*Id.* § 7.

tervening hearings. Notwithstanding their failure to pass into law, the bills and their attendant hearings effectively focused industry and official interest and firmly planted the tissue regulation question on the government's agenda. Responding to and harnessing this heightened interest level, the FDA took action, less than two months after the introduction of Senate Bill 1702 and House Bill 3547.

The Interim Rule Governing Human Tissue Intended for Transplantation

On December 14, 1993, the FDA issued an interim rule to address the public health concerns associated with tissue donation and transplantation.⁴³ This rule remains the most current government regulatory effort. Legal authority to create and enforce the regulation was drawn from section 361 of the Public Health Service Act: “[The Secretary] is authorized to make and enforce such regulations as in his judgment are necessary to prevent the spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.”⁴⁴ The authority to impose various enforcement options for violations of PHSA section 361 is found in section 368 and includes civil penalties and/or imprisonment of up to one year.⁴⁵

Given the gravity of the public health risk involved, the FDA bypassed normal notice and comment procedures for this regulation, deeming them “contrary to the public interest.” The agency found no acceptable excuse for failure

⁴³58 Fed. Reg. 65514 (1993) (to be codified at 21 C.F.R. pt. 1270).

⁴⁴42 U.S.C.S. § 264 (1996).

⁴⁵*Id.* § 271.

to perform the basic requirements of the rule, and hence elected to make them final and effective immediately.⁴⁶

The FDA’s justification for the interim rule was “the immediate need to protect the public health from the transmission of HIV infection and hepatitis infection through transplantation of tissue from donors infected with or at risk of these diseases.”⁴⁷ The Federal Register notice accompanying the rule emphasized that it was not meant to be a permanent or even long-term regulatory program, but that FDA intended to propose more extensive and permanent regulation in the near future. Nevertheless, as the current law in the area, the rule and its provisions merit careful description.⁴⁸

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Scope

The interim rule applies generally to anyone engaged in recovery, processing, or distribution of banked human tissue. Banked human tissue is defined as human tissue derived from one person intended for implantation into another, which has been handled and treated in ways not intended to alter its structure or functional characteristics. Any tissues treated only in ways to prevent transmission of disease are covered by the rule.⁴⁹

There are several significant categories of tissues, however, that are not af-

⁴⁶See 58 Fed. Reg. 65514, *supra* note 43, at 65518.

⁴⁷See 58 Fed. Reg. 65514, *supra* note 43, at 65516.

⁴⁸Citations in the description will be to the interim rule itself as it appears in the Code of Federal Regulations.

⁴⁹See 21 C.F.R. §§ 1270.1, 1270.3 (1996).

fectured by the interim rule. These include any tissues already regulated as drugs, biological products, or medical devices; vascularized organs; semen and other reproductive tissue; human milk; and bone marrow. Heart valve allografts, for example, since already regulated by FDA as a Class III medical devices, are not subject to the regulation. At bottom, then, tissues like bone, ligaments, tendons, cartilage, corneas, and skin whose structure is unchanged are those that are covered.⁵⁰

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Testing

The regulation mandates a battery of laboratory tests on the blood sample of any potential donor in order to prevent disease transmission. The tests include: HIV-1 antibody, HIV-2 antibody, hepatitis B surface antigen, and hepatitis C virus antibody.⁵¹ These are the only mandatory laboratory tests imposed by the statute and should be regarded as a regulatory floor. FDA noted that for certain tissue types there may be other desirable tests, but that such tests would have to be included in the subsequent permanent regulation and were inappropriate for an interim rule.⁵²

Further, the regulation requires that a process of determining suitable donors be used. The process must include an inquiry into the potential donor's medical

⁵⁰ *Id.*

⁵¹ See 21 C.F.R., *supra* note 49, § 1270.5.

⁵² See 58 Fed. Reg. 65514, *supra* note 43, at 65517.

history to determine if he has behaved so as to place himself in a high-risk category for contraction of HIV or hepatitis. No particular questions are specified as mandatory, however, as long as some sort of inquiry is conducted.⁵³ Again, the FDA suggested that a future rule might contain more precise instructions.

Quarantining of tissue is required for any tissue not accompanied by (1) negative laboratory results for the required tests, or (2) medical history demonstrating freedom from risk factors and other evidence of HIV or hepatitis infection.⁵⁴

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Written Procedures and Record-keeping

For both the disease testing process as well as the donor screening process, written procedures must be prepared and followed for all steps. Any deviation from these procedures must be documented and justified.⁵⁵ A new record-keeping system is also in operation, under which documentation is required of (1) the results and interpretation of all tests performed on a particular tissue, (2) the destruction or disposal of unsuitable tissue, and (3) the medical history of the donor as revealed by the screening process.⁵⁶ All such records must be maintained for at least ten years, due to the potentially long interval between in-

⁵³See *supra* note 51.

⁵⁴*Id.*

⁵⁵See 21 C.F.R., *supra* note 49, § 1270.7.

⁵⁶See 21 C.F.R., *supra* note 49, § 1270.11.

fection with HIV or hepatitis and manifestation of symptoms of either disease.⁵⁷

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Inspections and Enforcement

FDA inspection of tissue banking facilities is authorized, and covers the physical facility as well as all equipment, products, and records. Questioning of employees and handlers is also authorized. The inspections may be scheduled or unscheduled, and are restricted in scope to identifying facilities failing to take necessary precautions to prevent the spread of HIV and hepatitis.⁵⁸

If an inspector finds a violation of any of the interim rule's requirements, FDA is authorized to issue a written order mandating recall of the tissue and its destruction or other retention until its safety is confirmed. Alternatively, FDA may simply seize the violative tissue and destroy it. If a written order is issued, the recipient may within five days of receipt request a hearing on the matter.⁵⁹

Putting the Interim Rule to Work

The FDA's interim rule was a tremendous symbolic step, but its skeletal structure and deferral of several substantive issues to the "more permanent" regulation to come leave many practical questions unanswered. Without more

⁵⁷ See 21 C.F.R., *supra* note 49, § 1270.9.

⁵⁸ See 21 C.F.R., *supra* note 49, § 1270.13.

⁵⁹ See 21 C.F.R., *supra* note 49, § 1270.15.

particular guidance on exactly which tests must be run and which questions must be asked when screening donors, one could easily argue that the “standards” imposed by the interim rule are really not standards at all. The variance and complexity of scientific tests and blood collection algorithms available to identify HIV infection guarantee non-uniformity of result accuracy. The range of possible questions and interrogation techniques (written questionnaires, verbal interviews) to determine whether a potential donor exhibits risk factors for HIV or hepatitis infection similarly introduce a possibly dangerous element of uncertainty.

The Centers for Disease Control and the FDA responded to these concerns with a series of guidelines, workshops, and comment solicitations designed to aid tissue banks in carrying out their obligations under the interim rule consistently, safely, and effectively. Some were technical guidelines for proper tissue and blood sample tests to help standardize laboratory practice, others were suggestions about the most effective questions to ask in order to isolate risk-prone behavior in donors.⁶⁰ These efforts proved valuable to many in the industry, and helped provide much-needed standardization of procedures used to ensure the viability of donors and safety of donated tissue.

⁶⁰See, e.g., FDA CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, DRAFT DISCUSSION POINTS FOR SCREENING AND TESTING DONORS OF HUMAN TISSUE INTENDED FOR TRANSPLANTATION AND HUMAN REPRODUCTIVE TISSUE, AND FOR ESTABLISHMENT REGISTRATION (1995); 60 Fed. Reg. 27,406 (1995); FDA CENTER FOR BIOLOGICS EVALUATION AND RESEARCH, DRAFT DOCUMENT CONCERNING THE SCREENING AND TESTING OF DONORS OF HUMAN TISSUE INTENDED FOR TRANSPLANTATION PREPARED JUNE 12, 1995 (1995).

The interim rule has functioned reasonably well, as demonstrated by the absence since promulgation of any incident adversely affecting the public health at anywhere near the level of the Norwood revelation of 1991. Notwithstanding this success, a 1994 occurrence in California made it clear that weaknesses remained in the interim rule, underscoring the persistent necessity of more permanent government regulation of the field.

The incident involved a quantity of bone imported from Russia into California, much of which was inadequately screened. A wave of concern erupted with this revelation, and though upon investigation the FDA identified no incidence of disease directly traceable to the Russian bone, its questionable source prompted the FDA to nevertheless order its destruction.⁶¹

That such a quantity of transplantable bone could slip through regulation predictably touched off frustrated reactions and was cited by many as evidence that the industry needs tougher controls.

A pathologist at one California hospital who received the Russian bone expressed shock at the lack of controls. "The assumption was that anyone in the health-care industry is well-regulated, monitored and accredited," he told the *San Diego Union-Tribune*. "To find that there is a major segment that is not, is astounding."⁶² Clearly there remained significant pressure for more government regulation and faster FDA fulfillment of its promise to produce new, permanent

⁶¹ See Rex Dalton, *Half-Skeletons Target of Probe Here; San Diego Tissue Bank Distributed Questionable Bones for Transplants*, SAN DIEGO UNION-TRIB., Feb. 3, 1995, at A1.

⁶² *Id.*

regulations. This pressure has persisted to the present.

Recent Developments

Under strain from the medical community and the tissue banking industry, the FDA has endeavored to demonstrate that it has not been sitting on its hands. In a presentation to the AATB in September 1996, Mr. Steven Falter (director of FDA's CBER Regulation and Policy Division) explained several areas to be addressed in the final rule.⁶³

The final rule will likely be a combination of expansion of the interim rule and introduction of all-new regulations. Modifications to the interim rule will include: fifteen new definitions for clarification; requirements for determining donor suitability when next of kin cannot be contacted; better definition of testing parameters (*e.g.*, plasma dilution requirements); specification of parties responsible for record retention; more precise record-keeping requirements; identification protocols for facilities receiving or distributing tissues; administrative requirements for tissues offered for import; and exemption from routine inspection for hospitals and other establishments whose activities are limited to temporarily storing human tissues.⁶⁴

⁶³*FDA Considers Modifying Tissue Banking Regulations; Comments from Industry Will Be Encouraged*, TRANSPLANT NEWS, Sept. 17, 1996. (This is a secondary source for the substance of Mr. Falter's speech; the author was unable to acquire a transcript of the speech itself or of the AATB meeting; further, page numbers for *Transplant News* were unfortunately unavailable on-line.)

⁶⁴*Id.*

New regulatory requirements, many of which have been suggested by other agencies and the industry for quite some time, will likely include: annual registration of human tissue banks; creation and use of tissue tracking methods; and reporting of errors, accidents, or any transmission of infectious disease via human tissue. An interesting issue under consideration is an exemption for urgent medical circumstances and the associated definition thereof. The FDA is soliciting industry comment on which tissue types should be exempted and under what circumstances.⁶⁵

Other areas that new regulations might address are: requiring a six-month quarantine for semen donors; providing guidance on appropriate disposition of directed-donor cases⁶⁶ where the donor exhibits risk factors for infection; possible exemption for procedures where regulation would not enhance public health (*e.g.*, autologous tissue⁶⁷ transplantation); and finally, determining which transplantable substances should be treated as “human tissue” for regulatory purposes and which should be treated as medical devices or biological drugs.⁶⁸ This last concern would implicate the regulation of heart valve allografts, in many ways the issue that started this whole process and which has yet to be permanently decided.

⁶⁵ *Id.*

⁶⁶ When a tissue recipient specifies a particular donor from whom he wants the transplantable tissue to be harvested.

⁶⁷ Human cells that are taken from a patient biopsy, grown in cell culture, and then reimplanted into the same patient; this is distinguished from allogeneic tissue, which is from a donor source.

⁶⁸ See *FDA Considers Modifying Tissue Banking Regulations; Comments from Industry Will Be Encouraged*, *supra* note 63.

The FDA's research and ongoing dialogue with the tissue banking industry is noteworthy, but the all-important question of exactly when a new regulation will be issued remains uncertain. Some have argued that Republicans' control of Congress may delay further FDA action, since their agenda is not favorable to broadening FDA's role. Any decrease in the FDA's already tight budget makes the prospect of the agency's expanding regulation and enforcement obligations all the more unlikely.

Try, Try Again: the Human Tissues Safety Act of 1996

Notwithstanding the uncertainty about when, if ever, the FDA might issue its final rule, Senator Simon, (now) Senator Wyden, and Senator Dodd have continued in their efforts toward Congressional action. The three senators co-sponsored Senate Bill 2195, the Human Tissues Safety Act of 1996,⁶⁹ and introduced it in the Senate on October 3 of that year.

In his introductory speech, Senator Wyden blasted the current FDA system:

[I] find it shocking that FDA does not even have a list of the hundreds of tissue banks in this country that process human tissue from cadavers. Without such a list, FDA cannot send inspectors to these tissue banks to ensure that they comply with the Agency's infectious disease screening requirements. We should not wait until a child gets AIDS from infected tissue to empower FDA to ensure compliance. . . .⁷⁰

He also asserted that FDA policy with respect to autologous and allogeneic tissues was inconsistent with their respective risk levels. Requiring premarket

⁶⁹S. 2195, 104th Cong., 2d Sess. (1996).

⁷⁰142 CONG. REC. S12,309 (daily ed. Oct. 3, 1996) (statement of Sen. Wyden).

approval for some autologous tissues while essentially letting many allogeneic tissues go unregulated was, in Senator Wyden's opinion, "an exercise of trying to fit square pegs in round holes."⁷¹ The FDA's policy of continuing to regulate some tissues as medical devices also came under attack, as Senator Wyden asserted that human tissues "are not drugs, biological products, or medical devices, and . . . it is inappropriate to regulate them as if they were."⁷² Since human tissue is a nonproprietary substance, he argued, it is financially difficult for biotechnology companies to justify continued research when faced with the requirement of premarket approval.⁷³

Senate Bill 2195 proposes to address these problems by amending both the Food, Drug, and Cosmetic Act and the Public Health Service Act. First, it explicitly includes reproductive tissue, demineralized bone, heart valves, dura mater, and manipulated autologous cells in the definition of human tissue, while also excluding all human tissue (as so defined) from classification as a drug, biological product, or medical device.⁷⁴ As discussed above, both heart valves and dura mater are currently regulated by FDA as devices under the Medical Device Amendments of 1976.

Registration in accordance with section 510 of the Food, Drug, and Cosmetic Act is a prerequisite under the bill for engaging in any recovery, processing,

⁷¹ *Id.*

⁷² *Id.*

⁷³ *See id.*

⁷⁴ S.2195, 104th Cong., 2d Sess. § 1(a) (1996).

storage, or distribution of human tissue.⁷⁵ Further, the bill authorizes (but does not require) establishment by the Secretary of operating standards after notice and opportunity for comment. Any operating standards so established must be limited to infection control, processing practice, and labeling and record-keeping.⁷⁶

The bill also addresses advertising, and requires that any such promotional materials must consist only of “accurate and balanced representations that are consistent with sound scientific information. . . .”⁷⁷

Enforcement options under the bill are the most explicitly wide-ranging to date. They include inspection authority, orders of recall and/or destruction similar to those authorized by the interim rule, as well as the full range of civil, criminal, and seizure options like those afforded by the Human Tissue for Transplantation Act of 1993.

At the time this paper was completed, the most recent status of Senate Bill 2195 was that it had been read twice and referred to the Senate Committee on Labor and Human Resources. No further action had been taken as of January 16, 1996.

Lessons and Prospects for the Future

⁷⁵ *Id.* § 1(b).

⁷⁶ *Id.*

⁷⁷ *Id.*

In many ways the debate over regulation of human tissue is a classic case of government having to decide how much regulation is enough. On the one hand, government has an indisputable obligation to protect its citizens from unnecessary health risk. From this standpoint the failure to establish permanent, mandatory requirements for the most basic tests appears particularly egregious. The FDA's interim rule has attempted to remedy this particular problem, but as California residents could explain, the interim rule is only that - interim. It does not and should not be expected to provide comprehensive protection for tissue recipients. Its inadequacy, even its title, is a clear reminder that maximum safety will only be achieved through more permanent action, whether from FDA or from Congress.

On the other hand, no government program is without its costs. Increased enforcement and monitoring obligations would demand resources, and funding would likely come from private industry in the form of user fees. Such fees are likely to be passed on at least in part to the patient, and to the extent that they are not, they could quell scientific progress and inhibit breakthroughs that ironically may themselves lead to safer and less expensive treatment techniques.

This balancing of benefits, risks, and attendant costs is an enormously difficult one, particularly when the public health is at stake. The hearings, legislative attempts, and agency action during the last six years have shown that

government communication and cooperation with private industry is not only feasible but desirable. The debate is much more informed now than it was way back in 1991 after the Norwood tragedy. More importantly, although all parties involved disagree on some details, they agree that governmental oversight is appropriate to assure the public health in this area. Compromise will undoubtedly be necessary to effect meaningful change, but the progress of the last several years demonstrates that with continued perseverance and conscientious focus on the paramount goal of safety, such change is well within reach.